Methylnaltrexone Bromide Subcutaneous Injection
Criteria for Use
December 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. Local adjudication should be used until updated guidance and/or CFU are developed by the National PBM. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. ***THE CLINICIAN SHOULD USE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE OUTSIDE THE RECOMMENDATIONS SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.***

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria *If ANY item below applies, the patient should NOT receive methylnaltrexone subcutaneous injections.*

- ☐ Hypersensitivity to methylnaltrexone or product components
- ☐ Known or suspected mechanical gastrointestinal obstruction or other condition that may compromise drug action or cause bowel dysfunction (e.g., acute abdomen, ostomy, active diverticulitis, ischemic bowel, postsurgical adhesions, rectocele, intussusception, active peritoneal cancer such as ovarian cancer)
- ☐ Placement of peritoneal catheter for chemotherapy or dialysis (not studied)
- ☐ End-stage renal impairment on dialysis (not studied)
- ☐ Severe hepatic impairment / Child-Pugh grade C (not studied)
- ☐ Use of methylnaltrexone for *prevention* of opioid-induced constipation or impaction (no supporting evidence).
- ☐ Use of methylnaltrexone for postoperative ileus (preliminary results showed inefficacy).
- ☐ Use of methylnaltrexone for constipation that is not opioid-related (not studied)
- ☐ Concomitant use of other opioid antagonists (potential for increased risks of additive effects and opioid withdrawal)

Inclusion Criteria

For treatment of opioid-induced constipation in adults with chronic noncancer pain (all of the following must be met):

- ☐ Patient has been taking opioids for chronic noncancer pain for at least 4 weeks
- ☐ Intolerance or inadequate response to all of the following agents, unless there is a contraindication or risk factor(s) for serious adverse event(s):
    - □ One stimulant laxative (e.g., bisacodyl, sennosides), 1-month trial
    - □ MIRALAX (twice daily) or other osmotic laxative (e.g., sorbitol, magnesium (Mg) citrate, Mg hydroxide, glycerin rectal suppositories (RS)), 1-month trial
    - □ Naloxegol at optimized oral dosing, at least a 1-week trial (25 mg once daily in the morning on an empty stomach (consult Product Information for dosage adjustment recommendations for improving tolerability and for renal impairment)
    - □ Lubiprostone at optimized oral dosing; at least a 1-week trial (24 mcg twice daily orally with food and water; consult Product Information for dosage adjustment for hepatic impairment)

For treatment of opioid-induced constipation in patients with advanced illness (all of the following criteria must be met):

- ☐ Prescriber is a palliative care specialist or provider locally designated to prescribe methylnaltrexone
- ☐ Patient has advanced illness for which they are receiving palliative care in a monitored setting or at home with hospice care
- ☐ Patient has opioid-induced constipation, requires PROMPT laxative effects, and has had an insufficient response, contraindication, unmanageable intolerance, or route of administration limitation (e.g., dysphagia) to a laxative regimen consisting of at least usual doses (see table below) of an oral and / or rectal stimulant laxative (e.g., bisacodyl, sennoside), an oral and / or rectal stool softener (such as docusate), AND an oral osmotic laxative (such as lactulose or PEG 3350 in low doses).

Table 1. VANF Laxative Regimens

LAXATIVE	FORMULATION	INITIAL DOSE	USUAL DOSE	MAXIMUM DOSE
		(In divided doses, titrated to individual response)		
SENNOSIDES	Oral tablet	15 mg once daily	15–50 mg once or twice daily	70–100 mg in two divided doses
OR				
BISACODYL	Oral tablet	5 mg every 2–3 days	5–15 mg every 2–3 days	30 mg every 2–3 days
	Rectal suppository	10 mg every 2–3 days	10 mg every 2–3 days	10 mg every 2–3 days
PLUS				
DOCUSATE	Oral Capsule or Solution	50 mg once daily	50–360 mg in 1–4 divided doses	500 mg in 1–4 divided doses
	Rectal enema	Add 50-100 mg of docusate liquid (not syrup) to enema fluid (saline or water)		
AND				
LACTULOSE	Syrup	10 g (15 ml) once daily	10–20 g / day (15–30 ml / day) in 1–2 divided doses	60 ml / day in 1–2 divided doses
OR				
PEG 3350	Powder for solution, oral	17 g (about 1 heaping Tbsp) of powder mixed in 4–8 oz of water, juice, cola, or tea once daily for not longer than 2 weeks (OTC labeling). The OTC product labeling gives no limit on how frequently a course may be repeated. Under medical supervision, if the laxative response is insufficient, the dose may be increased to twice daily (off-label). Daily use (17 g/d) for constipation has been shown to be generally safe in otherwise healthy adults for up to one year.[†]		

OTC, Over-the-counter. [†] Center for Drug Evaluation and Research. MiraLax (Polyethylene Glycol 3350) Powder FDA Medical Review, 2006.

Dosing and Administration

FOR SUBCUTANEOUS INJECTION ONLY

Methylnaltrexone doses should be based on actual body weight and renal function as recommended in product information. Doses should be injected in the upper arm, abdomen, or thigh.

Actual Body Weight	Recommended Dosage	Injection Volume	Additional Dosing Guidance
Opioid-induced Constipation in Adults with Chronic Noncancer Pain			
Any weight	12 mg once daily	0.6 ml	Less frequent dosing (i.e., 12 mg every other day) was associated with higher incidences of adverse events and is not recommended. Maintenance laxative therapy should be discontinued before starting methylnaltrexone and may be resumed in patients who have OIC symptoms after taking methylnaltrexone for 3 days. Patient should be within close proximity to toilet facilities once a dose is administered
Opioid-induced Constipation in Adults with Advanced Illness			
38 to less than 62 kg (84 to less than 136 lb)	8 mg every 48 hours as needed (*p.r.n.)*	0.4 ml	Doses may be given at longer intervals as needed. Responders will typically have a bowel movement after at least one of the first three doses. If there is no laxation response after 7 d (3 doses), the patient is unlikely to respond to additional doses and methylnaltrexone should be discontinued. A maximum of 2 doses may be given 24 hours apart *p.r.n.* However, the need for dosing every 24 hours is exceptional, and the second dose should be given only if the previous day's dose is ineffective. Thereafter, resume dosing every 48 hours.
62 to 114 kg (136 to 251 lb)	12 mg every 48 hours as needed (*p.r.n.)*	0.6 ml	
Outside of ranges shown above (Less than 38 kg or more than 114 kg)	0.15 mg / kg every 48 hours as needed (*p.r.n.)**	0.0075 ml / kg (Round to nearest 0.1 ml)	
Severe Renal Impairment			
CrCl less than 30 ml / min	Reduce dose by 50%*****		

* Use single-use vials (which allow dose modification) rather than the single-use prefilled syringes that deliver fixed doses.

End-stage renal impairment requiring dialysis: Not studied

Mild or moderate hepatic impairment (Child-Pugh class A or B): No dosage adjustment necessary

Severe hepatic impairment: Pharmacokinetics not studied

Monitoring

Opioid-induced constipation in adults with chronic noncancer pain: Re-evaluate the need for continuing methylnaltrexone when the opioid regimen is changed to avoid adverse effects.

Opioid-induced constipation in patients with advanced illness: Patients who develop severe or persistent diarrhea after receiving methylnaltrexone should be monitored closely for dehydration.

Gastrointestinal Perforation: Monitor for the development of severe, persistent or worsening abdominal pain, and discontinue methylnaltrexone and other laxatives in patients who develop this symptoms.

Severe or Persistent Diarrhea: Advise patients to discontinue methylnaltrexone and consult their health care provider if severe or persistent diarrhea occurs.

Opioid Withdrawal and/or Reduced Analgesia: Patients with disruptions to the blood-brain barrier may be at increased risk for opioid withdrawal and/or reduced pain control. Weigh risk-benefits. Monitor for loss of analgesia and for opioid withdrawal symptoms such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety and yawning.

Issues for Consideration

FDA-approved Indications:

- Treatment of opioid-induced constipation in adult patients with chronic noncancer pain.
- Treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient. Use of methylnaltrexone subcutaneous injections beyond 4 months has not been studied.

General treatment considerations for opioid-induced constipation:

- Bulk forming laxatives are relatively contraindicated in opioid-induced constipation. A stool softener (e.g., docusate) is considered to be of low benefit and low harm for opioid-induced constipation and may be used but is not required prior to use of methylnaltrexone for opioid-induced constipation.
- Use the more cost-effective agent(s) for initial therapy.
- Therapeutic trials of the orally administered agents naloxegol and lubiprostone may be preferred before daily methylnaltrexone injections because of better ease and comfort of administration.

Treatment of opioid-induced constipation in adults with chronic noncancer pain:

- ***Use of laxatives after initiation of methylnaltrexone therapy:*** Although maintenance laxative therapy should be discontinued before starting methylnaltrexone, laxative(s) can be used as needed if there is a suboptimal response to methylnaltrexone after 3 days.
- Sustained exposure to opioids prior to starting methylnaltrexone may increase the patient's sensitivity to the effects of methylnaltrexone.
- Methylnaltrexone therapy was associated with adverse events that may have been symptoms of opioid withdrawal. These symptoms included abdominal pain, nausea, diarrhea, hyperhidrosis, hot flush, tremor and chills.

Treatment of opioid-induced constipation in patients with advanced illness:

- Opioid-induced constipation in patients with advanced illness may be defined as either fewer than three bowel movements in the preceding week or no bowel movement for 2 days.
- Chronic daily stimulant-based laxative regimens should be continued and optimized in addition to using methylnaltrexone as needed. There is no evidence to support use of methylnaltrexone as monotherapy.
- Bulk laxatives are not recommended for opioid-induced constipation in palliative care patients because such patients are unlikely to maintain adequate hydration to prevent fecal impaction and bowel obstruction.
- The efficacy of methylnaltrexone was shown when it was added on to usual two- to three-drug laxative therapy.
- There is a lack of evidence to support treatment in patients other than those with advanced illness receiving palliative care.
- Duration of drug exposure in clinical trials and safety data are limited. Safety beyond 4 months of treatment has not been established; therefore, duration of treatment should be limited.

Pregnancy: Category C. Methylnaltrexone has not been adequately studied in pregnant women. There is a possibility that methylnaltrexone can precipitate opioid withdrawal in a fetus because of an immature fetal blood brain barrier. Use methylnaltrexone during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Mothers. Whether methylnaltrexone is present in human milk is unknown. Serious adverse effects, including opioid withdrawal, may occur in nursing infants. Discontinue methylnaltrexone or discontinue nursing, taking into account the importance of therapy to the mother.

Geriatric Use. Some older individuals may have greater sensitivity to methylnaltrexone. No age-based dosage adjustment is recommended.

Refills and Renewal Criteria

For treatment of opioid-induced constipation in adults with chronic noncancer pain

- ☐ Patient experiences clinically important benefit (i.e., improved constipation and abdominal pain) after an adequate therapeutic trial (1 week) and tolerates treatment.
- ☐ Maximum duration of treatment is 12 months (48 weeks) unless there is documentation of patient benefits, acceptable risks, AND need for continuing subcutaneous methylnaltrexone therapy (beyond 12 months).

For treatment of opioid-induced constipation in patients with advanced illness:

- ☐ Limit of 3 doses and no refills for the initial prescription at recommended alternate-day dosing.
- ☐ Documentation of patient benefit after at least one of the initial 3 doses (given once every other day p.r.n.) is required for subsequent refillable prescriptions.
- ☐ Maximum duration of treatment is 4 months unless there is documentation of patient benefits, acceptable risks, AND need for continuing subcutaneous methylnaltrexone therapy (beyond 4 months) despite optimization of the patient's chronic stimulant-based laxative regimen.

Revised December 2015. Original: March 2010. Contact: Francine Goodman, PharmD, BCPS, National Clinical Pharmacy Program Manager – Formulary. VA Pharmacy Benefits Management Services (10P4P)